## APPENDIX A

## Version to Show Changes Made

- A chimeric peptide comprising <u>a μ</u> [an N-terminal] opioid receptor binding moiety <u>at its</u>
   N-terminus and [a C-terminal] <u>an agonist</u> Substance P receptor [agonist] binding moiety <u>at its C-terminus</u>, wherein said peptide induces analgesia.
- 28. The peptide of claim [27] 1, wherein said opioid receptor binding moiety is a μ receptor agonist.
- The peptide of claim 30 wherein said opioid receptor binding moiety is [selected from the group consisting of peptides] a peptide having any one of SEQ ID Nos: 1-11, or an N-terminal [fragments and] fragment or N-terminal [derivatives] derivative thereof.
- 32. The peptide of claim 30 wherein said opioid receptor binding moiety is endomorphin 1, endomorphin 2, an N-terminal [fragment] fragment, or an N-terminal derivative thereof.
- The peptide of claim 32 wherein said opioid receptor binding moiety is [selected from the group consisting of peptides] a peptide having [SEQ ID Nos: 2-3] SEQ ID No: 2 or 3, or an N-terminal [fragments and] fragment or N-terminal [derivatives] derivative thereof.
- The peptide of claim 1, [24 or 25] wherein said <u>agonist</u> Substance P receptor [agonist] binding moiety comprises Substance P, a C-terminal Substance P [fragment] <u>fragment</u>, or a C-terminal Substance P derivative.
- 46. The peptide of claim 1, [24 or 25] wherein the –COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is protected.

Page 28 of 38

Attorney Docket No.: 2004117-0002 Client Reference No.: NEMC 197

- 49. The peptide of claim 48 wherein said Substance P receptor binding moiety is [selected from the group consisting of peptides] a peptide having any one of SEQ ID Nos: 21, 36 and 38-41, or a C-terminal [N-terminal fragments and] fragment or C-terminal [N-terminal derivatives] derivative thereof.
- 53. The peptide of claim 52 wherein said Substance P receptor binding moiety is [selected from the group consisting of peptides] a peptide having any one of SEQ ID Nos: 25-27, or a C-terminal [N-terminal fragments and] fragment or C-terminal [N-terminal derivatives] derivative thereof.
- 56. The peptide of claim 55 wherein said Substance P receptor binding moiety is [selected from the group consisting of peptides] a peptide having any one of SEQ ID Nos: 28-30, or a C-terminal [N-terminal fragments and] fragment or C-terminal [N-terminal derivatives] derivative thereof.
- 57. The peptide of claim 1 wherein the opioid receptor binding moiety is [selected from the group consisting of] endomorphin 1, endomorphin 2, or an N-terminal [fragments and] fragment or N-terminal [derivatives] derivative thereof; and the Substance P receptor binding moiety is [selected from the group consisting of] Substance P, or a C-terminal [fragments and] fragment or C-terminal [derivatives] derivative thereof.
- 61. The peptide of claim [60] 1 wherein said peptide comprises at least one D-amino acid.
- 64. The <u>pharmaceutical</u> composition of claim 62, wherein said peptide induces analgesia when administered to a mammal.
- 69. The <u>pharmaceutical</u> composition of claim [68] <u>62</u>, wherein said opioid receptor binding moiety is a μ receptor agonist.

- 70. The <u>pharmaceutical</u> composition of claim 69 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is a free amine.
- 71. The <u>pharmaceutical</u> composition of claim 70 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is Tyr.
- 72. The <u>pharmaceutical</u> composition of claim 71 wherein said opioid receptor binding moiety is [selected from the group consisting of peptides] <u>a peptide</u> having <u>any one of SEQ ID</u>
  Nos: 1-11, <u>or an N-terminal [fragments and] fragment or N-terminal [derivatives]</u>
  derivative thereof.
- 73. The <u>pharmaceutical</u> composition of claim 71 wherein said opioid receptor binding moiety is endomorphin 1, endomorphin 2, an N-terminal [fragment] <u>fragment</u>, or <u>an N-terminal</u> derivative thereof.
- 74. The <u>pharmaceutical</u> composition of claim 73 wherein said opioid receptor binding moiety is [selected from the group consisting of peptides] <u>a peptide</u> having [SEQ ID Nos: 2-3] <u>SEQ ID No: 2 or 3, or an N-terminal [fragments and] fragment or N-terminal [derivatives] derivative</u> thereof.
- 86. The <u>pharmaceutical</u> composition of claim 62, [65 or 66] wherein said <u>agonist</u> Substance P receptor [agonist] binding moiety comprises Substance P, a C-terminal Substance P [fragment] <u>fragment</u>, or a C-terminal Substance P derivative.
- 87. The <u>pharmaceutical</u> composition of claim 62, [65 or 66] wherein the -COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is protected.

- 88. The <u>pharmaceutical</u> composition of claim 87 wherein the -COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is amidated.
- 89. The <u>pharmaceutical</u> composition of claim 88 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Met-NH<sub>2</sub>.
- 90. The <u>pharmaceutical</u> composition of claim 89 wherein said Substance P receptor binding moiety is [selected from the group consisting of peptides] <u>a peptide</u> having <u>any one of SEQ ID Nos: 21, 36 and 38-41, or a C-terminal</u> [N-terminal fragments and] <u>fragment or C-terminal</u> [N-terminal derivatives] <u>derivative</u> thereof.
- 91. The <u>pharmaceutical</u> composition of claim 87 wherein the -COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is esterified.
- 92. The <u>pharmaceutical</u> composition of claim 91 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is a methyl ester.
- 93. The <u>pharmaceutical</u> composition of claim 92 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Gly-OMe, Lys-COOMe or Arg-COOMe.
- 94. The <u>pharmaceutical</u> composition of claim 93 wherein said Substance P receptor binding moiety is [selected from the group consisting of peptides] <u>a peptide</u> having <u>any one of SEQ ID Nos: 25-27, or a C-terminal</u> [N-terminal fragments and] <u>fragment or C-terminal</u> [N-terminal derivatives] <u>derivative</u> thereof.
- 95. The <u>pharmaceutical</u> composition of claim 91 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is an ethyl ester.

- 96. The <u>pharmaceutical</u> composition of claim 95 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Gly-COOEt, Lys-COOEt or Arg-COOEt.
- 97. The <u>pharmaceutical</u> composition of claim 96 wherein said Substance P receptor binding moiety is [selected from the group consisting of peptides] <u>a peptide</u> having <u>any one of SEQ ID Nos: 28-30, or a C-terminal [N-terminal fragments and] fragment or C-terminal [N-terminal derivatives] <u>derivative</u> thereof.</u>
- 98. The <u>pharmaceutical</u> composition of claim 62 wherein the opioid receptor binding moiety is [selected from the group consisting of] endomorphin 1, endomorphin 2, <u>or an</u> N-terminal [fragments and] <u>fragment or</u> N-terminal [derivatives] <u>derivative</u> thereof; and the Substance P receptor binding moiety is [selected from the group consisting of] Substance P, <u>or a</u> C-terminal [fragments and] <u>fragment or</u> C-terminal [derivatives] <u>derivative</u> thereof.
- 99. The pharmaceutical composition of claim 62 wherein the peptide has SEQ ID No: 42.
- 100. The pharmaceutical composition of claim 62 wherein the peptide has SEQ ID No: 43.
- 102. The <u>pharmaceutical</u> composition of claim [101] <u>62</u> wherein said peptide comprises at least one D-amino acid.